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Monte Carlo-Simulated Annealing Computational Studies of the Bovine Rhodopsin-Arrestin Complex, Including Three Mutation Studies of Key Residues

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The group of proteins collectively called arrestin is involved in the quenching of a wide variety of G protein-coupled receptors, including the rod specific visual pigment rhodopsin. In the case of rhodopsin, this is thought to be facilitated by phosphorylated residues on the carboxyl-terminal rhodopsin tail. In an attempt to understand the role of phosphorylated residues in this complex process, we studied the interaction of the rhodopsin carboxyl tail (20 residues) with the basal state of the rod specific arrestin protein (R-Arrestin) (1CF1.pdb). We began with an all atom energy minimized (Amber-like force field) R-arrestin structure and an all atom energy minimized unphosphorylated (wild type) rhodopsin Tail (1HZX.pdb). We then utilized a Monte Carlo Simulated Annealing (MC-SA) algorithm (all atom Amber-like force field) to study the conformational energetic of the rhodopsin-arrestin complex. In our simulations, all atoms of the entire rhodopsin-arrestin complex are allowed to move, and new conformations are generated based on an energy-minimizing criterion (MC-SA algorithm). In order to perform an extended search of the possible conformational space available to the rhodopsin tail, 15 MC-SA simulations were preformed over a temperature range from 300 K to 50 K. Because we are not able to simulate the phosphorylated rhodopsin tail directly, we preformed three key mutational studies. All serine and threonine residues were mutated to: (1). aspartic acid. (2). glutamic acid and (3). alanine. This computational work will be compared to the concurrent *in vitro* biochemical studies using rhodopsin molecules with similar cytoplasmic-tail mutants. The MC-SA studies of the wild type complex and mutated complexes allowed us to determine the role of the charge-charge interactions between the rhodopsin carboxyl-tail and the R-arrestin complex. We find that this charge-charge interaction may be a significant first step for the arrestin quenching mechanism.